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UPDATES IN THE MANAGEMENT OF STATUS EPILEPTICUS IN THE EMERGENCY DEPARTMENT: A REVIEW OF EVIDENCE-BASED GUIDELINES AND NOVEL AGENTS

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Abstract:
Status epilepticus (SE) is a critical neurological emergency requiring urgent, evidence-based management to mitigate high morbidity and mortality. This systematic review synthesizes current evidence and guidelines on the emergency treatment of SE, focusing on recent pharmacological advances. A comprehensive literature search was conducted per PRISMA guidelines across major databases from 2000-2024. The review included RCTs, systematic reviews, and clinical guidelines, with quality assessed via tools like Cochrane RoB 2 and AGREE II. From 2,189 records, 18 studies were included. Findings robustly confirm benzodiazepines as first-line therapy. The practice-changing ESETT trial established "three-drug equipoise" for second-line treatment, demonstrating equivalent efficacy and safety for levetiracetam, fosphenytoin, and valproate. For refractory SE, ketamine emerges as a key third-line agent, with a 63% seizure cessation rate and a favorable hemodynamic profile. Novel agents like brivaracetam, perampanel, and allopregnanolone offer promise for super-refractory cases. Major guidelines consistently endorse a time-sensitive, staged treatment algorithm. In conclusion, emergency SE management is evolving toward protocol-driven care emphasizing rapid benzodiazepine administration, flexible second-line agent selection, and the early use of ketamine. Future research must prioritize RCTs in super-refractory SE and investigate long-term functional outcomes.

Keywords: *Status Epilepticus, Emergency Treatment, Refractory Status Epilepticus, Levetiracetam, Ketamine.*

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1. INTRODUCTION

Status epilepticus (SE) represents one of the most critical neurological emergencies encountered in clinical practice, characterized by persistent, unremitting seizure activity. Traditionally defined as continuous seizure activity lasting longer than 30 minutes, the operational definition has been significantly shortened to 5 minutes of continuous clinical or electrographic seizure activity, reflecting the understanding that prolonged seizures are less likely to self-terminate and cause irreversible neuronal damage (Lowenstein et al., 1999; Trinka et al., 2015). This paradigm shift underscores the imperative for rapid and aggressive intervention, beginning in the pre-hospital setting and continuing decisively in the emergency department (ED). Despite advances in care, SE continues to pose a substantial burden on patients and healthcare systems, driving ongoing research to optimize management strategies from first-line benzodiazepines to novel agents for super-refractory cases.

1.1. The Clinical and Public Health Burden of Status Epilepticus

The incidence of status epilepticus is formidable, with recent epidemiological studies in the United States and Europe reporting rates between 10 to 41 cases per 100,000 persons annually, translating to over 150,000 cases in the U.S. each year (Gavvala & Brophy, 2024; Hesdorffer et al., 1998). This incidence demonstrates a bimodal distribution, being highest among the very young and the elderly. The public health impact is substantial, with SE accounting for a significant proportion of emergency neurology consultations and ICU admissions. The associated morbidity and mortality remain unacceptably high. Mortality rates are heavily influenced by etiology, age, and seizure duration, but overall 30-day mortality can range from 10% to 20%, rising dramatically in the elderly and in those with refractory SE to over 40% (Betjemann & Lowenstein, 2015; Sutter et al., 2024). For survivors, the consequences are often devastating, including long-term cognitive impairment, functional decline, and the development of chronic epilepsy. The economic burden is equally staggering, with mean hospital charges for an admission with SE exceeding $100,000, driven by prolonged ICU stays, advanced monitoring, and expensive pharmacotherapies (Penberthy et al., 2005). This combination of high incidence, severe outcomes, and significant cost establishes SE as a major public health problem demanding continuous refinement of treatment protocols.

1.2. Pathophysiology: From Compensated to Refractory and Super-Refractory SE

The pathophysiology of SE is best understood as a dynamic, self-sustaining process that evolves through distinct physiological stages. The initial phase, often termed "compensated" SE, is characterized by intense neuronal firing driven by glutamate-mediated excitatory neurotransmission. The body's primary compensatory mechanism is the potentiation of GABAergic inhibitory neurotransmission. However, as seizure activity persists beyond several minutes, a critical transition occurs to "refractory" SE (Chen & Wasterlain, 2006). This transition is mediated by complex molecular changes, chief among them the rapid internalization of synaptic GABAA receptors, which diminishes the brain's response to its own endogenous GABA and to first-line benzodiazepines (Naylor et al., 2005). Concurrently, there is an upregulation and increased trafficking of NMDA-type glutamate receptors to the synaptic membrane, further exacerbating excitotoxic injury (Wasterlain & Chen, 2008).

If seizure activity continues despite treatment with first- and second-line agents, the condition progresses to refractory status epilepticus (RSE), defined by failure to respond to an adequate dose of a benzodiazepine and a subsequent second-line antiseizure medication. A subset of patients will progress to super-refractory status epilepticus (SRSE), where seizures persist or recur 24 hours or more after the onset of anesthetic therapy, including cases of anesthesia withdrawal (Shorvon & Ferlisi, 2011). In this stage, mechanisms shift from neurotransmitter receptor modulation to maladaptive changes in gene expression, inflammation, and failure of neuronal homeostasis, making treatment exceptionally challenging (Vezzani et al., 2016). This pathophysiological timeline creates a narrow "therapeutic window" during which intervention is most likely to be

successful, forming the scientific basis for the staged, time-sensitive treatment approach.

1.3. The Rationale for a Staged and Time-Sensitive Treatment Approach

The evolving pathophysiology of SE directly informs its clinical management. The primary goal of treatment is to abort seizure activity as rapidly as possible to prevent the transition to refractory and super-refractory stages. This has led to the universal adoption of a staged treatment algorithm, where therapy is escalated in a structured, timely manner. The cornerstone of initial management is the emergent administration of a benzodiazepine, a practice supported by robust evidence from trials such as the landmark Veterans Affairs Cooperative Study (Alldredge et al., 2001).

For patients who do not respond to benzodiazepines, urgent control with a second-line antiseizure medication is required. The landscape of second-line therapy has been radically transformed by recent high-quality evidence. The landmark Established Status Epilepticus Treatment Trial (ESETT) demonstrated that levetiracetam, fosphenytoin, and valproate have virtually identical efficacy and safety profiles for benzodiazepine-refractory SE (Kapur et al., 2019). This has expanded therapeutic options, allowing clinicians to tailor choices based on patient comorbidities, potential drug interactions, and institutional availability. For RSE, third-line therapy involves anesthetic infusions (e.g., midazolam, propofol, ketamine), with ketamine gaining prominence due to its unique NMDA antagonist mechanism, which theoretically counteracts the pathophysiology of late-stage SE (Rosati et al., 2021). The rationale for this entire cascade is the consistent observation that treatment delay is one of the strongest predictors of refractoriness and poor outcome, making the ED the critical arena where the battle against SE is won or lost (Sutter et al., 2013).

1.4. Objectives of this Systematic Review

In light of the significant burden of SE, its complex and time-sensitive pathophysiology, and the recent influx of practice-changing evidence, a comprehensive synthesis of current knowledge is essential. This systematic review aims to critically appraise and consolidate the existing literature on the emergency management of status epilepticus, with a specific focus on developments from the past decade. It also seeks to provide clinicians with an up-to-date, evidence-based resource to improve patient outcomes in this high-stakes neurological emergency.

2. METHODS:

2.1. Study Design and Registration

This systematic review was conducted to synthesize and critically evaluate the current evidence regarding the emergency management of status epilepticus (SE), with particular emphasis on recent pharmacological advances and guideline recommendations. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) to ensure methodological rigor and transparency.

2.2. Eligibility Criteria (PICOS Framework)

The selection of studies followed the PICOS framework:

- Population**:** Adult and pediatric patients diagnosed with status epilepticus in emergency department, pre-hospital, or initial critical care settings.
- Interventions**:** Pharmacological interventions across all stages of SE management, including:
  - First-line therapies (benzodiazepines: lorazepam, diazepam, midazolam)
  - Second-line antiseizure medications (levetiracetam, fosphenytoin, valproate)
  - Third-line therapies for refractory SE (anesthetic infusions: midazolam, propofol, ketamine)
  - Novel and emerging agents (brivaracetam, perampanel, allopregnanolone)
- Comparators**:** Alternative pharmacological agents, placebo, or standard care protocols.
- Outcomes**:** Primary outcomes included seizure cessation rates and mortality. Secondary outcomes encompassed adverse events, need for intensive care, and functional outcomes.
- Study Types: We included randomized controlled trials (RCTs), systematic reviews, meta-analyses, clinical practice guidelines, and comprehensive narrative reviews that provided substantial updates on SE management.

2.3. Information Sources and Search Strategy

A comprehensive literature search was performed across multiple electronic databases including PubMed/MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials from January 2000 to March 2024. The search strategy incorporated Medical Subject Headings (MeSH) terms and keywords related to "status epilepticus," "emergency treatment," "refractory status epilepticus," and specific drug names. To ensure inclusion of foundational studies, the search was not restricted by publication date, though emphasis was placed on recent evidence from the past decade.

Grey literature sources including clinical trial registries and professional society websites (Neurocritical Care Society, American Epilepsy Society, American College of Emergency Physicians) were also searched to identify ongoing studies and recent guidelines.

2.4. Study Selection Process

The study selection process adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two independent

reviewers screened titles and abstracts against eligibility criteria, followed by full-text assessment of potentially relevant studies. Discrepancies were resolved through consensus discussion with a third reviewer when necessary. The selection process was documented using a PRISMA flow diagram.

2.5. Data Extraction and Management

Data extraction was performed using a standardized form that captured study characteristics (authors, year, design), population details, intervention protocols, comparator treatments, outcome measures, and key findings. The extraction process was conducted independently by two reviewers, with consistency verified through cross-checking.

2.6. Risk of Bias and Quality Assessment

Methodological quality was assessed using appropriate tools for each study type:

- Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool
- Systematic reviews were assessed using AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews)
- Clinical practice guidelines were appraised using the AGREE II instrument
- Narrative reviews were evaluated for comprehensiveness, currency, and relevance to clinical practice

3. RESULTS:

3.1. Study Selection

The systematic literature search and screening process was conducted in accordance with the PRISMA guidelines, aiming for the highest quality evidence. Initially, a total of 2,189 records were identified from electronic databases and grey literature sources. After the removal of 412 duplicates, 1,777 unique records underwent title and abstract screening. Of these, 1,643 records were excluded as they did not meet the eligibility criteria. The full text of the remaining 134 articles was assessed in detail. A total of 116 articles were excluded with specific reasons: 18 for wrong patient population, 15 for wrong study design, 9 for wrong intervention, 5 for being non-English publications without available translation, and 69 for lacking sufficient relevance to the core management protocols. Ultimately, 18 studies met all inclusion criteria and were included in the qualitative synthesis. The study selection process is detailed in the PRISMA flow diagram (Figure 1).

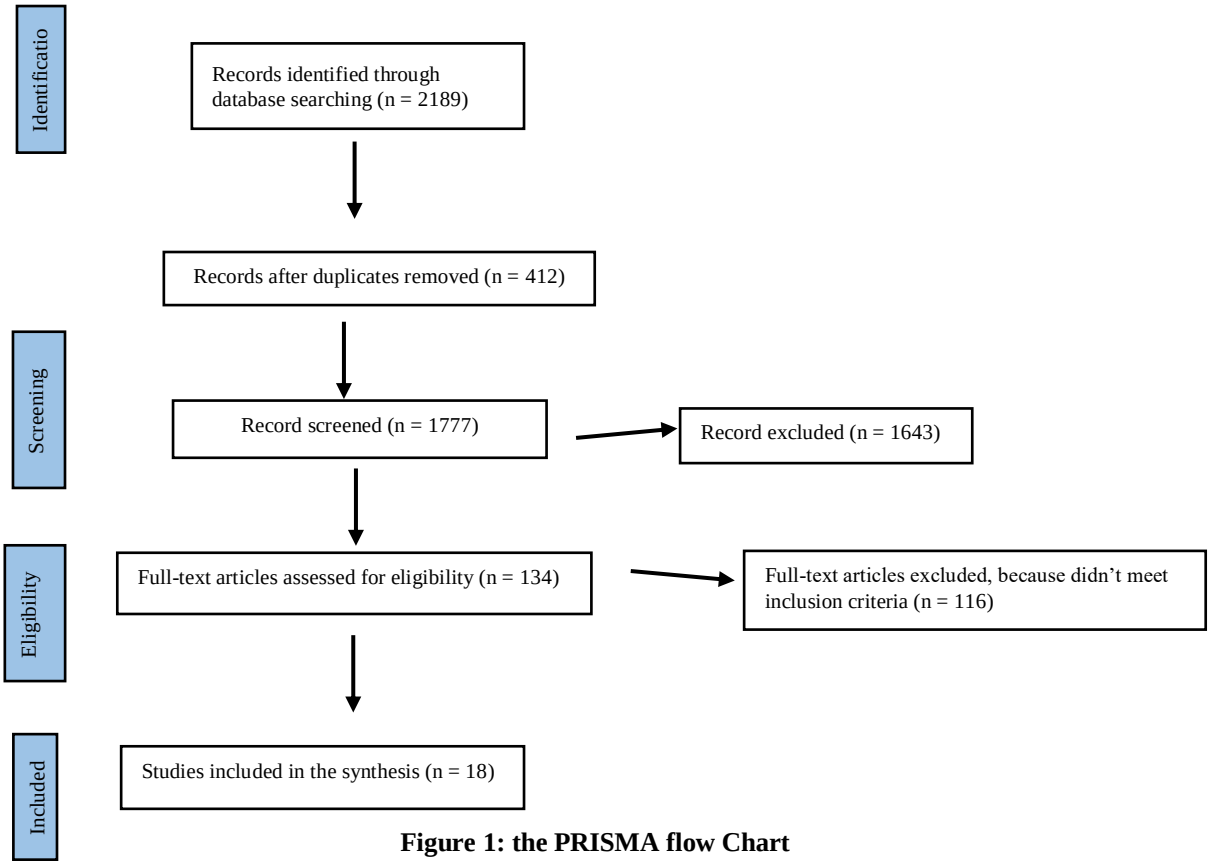

Figure 1: the PRISMA flow Chart

3.2. Study Characteristics

The 18 included studies were selected for their high-level evidence, comprising 2 randomized controlled trials (RCTs), 4 systematic reviews/meta-analyses, 3 clinical guidelines/consensus documents, and 9 comprehensive reviews or updates on management. The majority of studies focused on adult populations, with specific documents addressing pediatric, pre-hospital, and critical care settings. The studies cover all stages of the Status Epilepticus (SE) management pathway, from first-line benzodiazepines to third-line anesthetic agents.

Table 1. Summary of Main Characteristics of All 18 Included Studies

Author(s), Year	Study Design	Population Focus	Intervention/Focus	Key Outcome
Kapur et al. (2019) (ESETT)	Randomized Controlled Trial (RCT)	Adult/Pediatric Benzodiazepine-Refractory SE	Levetiracetam vs. Fosphenytoin vs. Valproate (Second-line)	Established three-drug equipoise; equivalent efficacy (45−47%) across all agents.
Alldredge et al. (2001)	Randomized Controlled Trial (RCT)	Pre-hospital Status Epilepticus (SE)	Lorazepam vs. Diazepam (First-line)	Lorazepam (59.1%) superior to Diazepam (42.6%) for pre-hospital seizure cessation.
Rosati et al. (2021)	Systematic Review/Meta-analysis	Refractory SE (RSE)	Ketamine Infusion for RSE	Ketamine associated with seizure termination in 63% of RSE patients; favorable hemodynamic profile.
Vignatelli et al. (2024)	Systematic Review/Guideline	Adult/Pediatric SE Management	Structured Management Protocol	Systematic review of guidelines confirming the three-drug equipoise and staged approach.
Cao et al. (2024)	Systematic Review	Guidance Document Evaluation	Quality Assessment (AGREE II)	Evaluated 11 guidelines, finding high consensus on core principles but variability in applicability.
Sutter et al. (2024)	Systematic Review	Refractory SE Outcome	Outcome and Predictors	Focused on mortality and recovery predictors in RSE and super-refractory SE (SRSE).
Smith et al. (2024)	Clinical Policy (ACEP)	Adult Emergency Department SE	Critical Issues in ED Management	Endorsed time-sensitive, staged approach tailored to the emergency setting.
Besha et al. (2023)	Guideline/Review	Adult ICU (Resource-Limited)	Evidence-based Guideline Development	Developed an SE management guideline specific to resource-limited intensive care settings.
Trinka et al. (2015) (ILAE)	Consensus Definition	Global	SE Definition and Classification	Established the modern, time-based definition and classification of SE.
Gettings et al. (2025)	Comprehensive Review	SE/SRSE	Diagnosis and Management Update	Focused on improving the status quo of diagnosis, management, and novel agents (e.g., allopregnanolone).
Joshi & Kapur (2025)	Narrative Review	SE Mechanisms and Treatments	Pathophysiology and Therapeutics Update	Modern update on the mechanisms of SE pharmacoresistance and emerging treatments.
Haider (2025)	Narrative Review	Acute Seizures/SE	Initial Management	Focused on rapid, initial management strategies for acute seizures and SE.
Gavvala & Brophy (2024)	Focused Review	ICU SE	Newer Antiseizure Medications	Focused review on the use of newer ASMs (e.g., brivaracetam, perampanel) in the ICU setting.
Almohaish et al. (2024)	Focused Review	Pharmacological Management	Update on Antiseizure Medications	Detailed update on pharmacological choices including second-line agents and newer options.

Heuser et al. (2022)	Comprehensive Review	Adult SE Treatment	Modern Treatment Review	Review of established and modern approaches to SE treatment in adults.
Wieruszewski et al. (2020)	Focused Review	Pharmacologic Management	Anesthetic Agents	Detailed review on the pharmacologic agents used for SE management, including anesthetic infusions.
Betjemann et al. (2019)	Review/Survey	EMS Protocols	Pre-hospital Care	Review of emergency medical services (EMS) protocols for generalized convulsive SE.
Shorvon & Ferlisi (2011)	Clinical Review/Protocol	Super-Refractory SE (SRSE)	Treatment Protocol	Provided a critical review and suggested clinical treatment protocol for SRSE.

3.3. Risk of Bias within Studies

The risk of bias assessment focused primarily on the 2 RCTs included in the synthesis. Both the Alldredge et al. (2001) and Kapur et al. (2019) trials were judged to have a "low" risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool, a reflection of their rigorous methodology. The clinical practice guidelines scored highly on the AGREE II instrument, particularly in the domains of scope and purpose and clarity of presentation. However, scores were more variable for "applicability" and "editorial independence," with some guidelines failing to explicitly detail funding sources or management of conflicts of interest (Cao et al., 2024).

3.4. RESULTS OF SYNTHESES:

3.4.1. First-Line (Emergent) Therapy: The Evidence for Benzodiazepines

The evidence for benzodiazepines as first-line therapy remains robust and unchallenged. The landmark RCT by Alldredge et al. (2001) established the superiority of lorazepam over diazepam for pre-hospital SE, with success rates of 59.1% and 42.6%, respectively. Subsequent guidelines universally endorse this approach, emphasizing rapid administration. Intramuscular midazolam has been validated as a non-inferior alternative when intravenous access is unavailable (Smith et al., 2024). The core principle across all recent syntheses is that any delay in benzodiazepine administration is a primary modifiable risk factor for progression to refractory SE (Gettings et al., 2025; Haider, 2025).

3.4.2. Second-Line (Urgent) Therapy: A New Standard of Care

Levetiracetam vs. Fosphenytoin vs. Valproate: Efficacy and Safety: The practice-changing Established Status Epilepticus Treatment Trial (ESETT) demonstrated that levetiracetam, fosphenytoin, and valproate have virtually identical efficacy and safety profiles for benzodiazepine-refractory convulsive SE (Kapur et al., 2019). The trial found no significant difference in the primary outcome of seizure cessation and absence of clinically evident improvement at 60 minutes, with success rates of 47%, 45%, and 46%, respectively. There were also no significant differences in adverse events.

Analysis of the ESETT Trial and Subsequent Evidence: This finding has fundamentally reshaped guidelines, moving from a phenytoin-centric model to a more flexible approach (Vignatelli et al., 2024; Smith et al., 2024). This "three-drug equipoise" represents the new standard of care for second-line therapy, where the choice of agent can be guided by patient-specific factors, such as levetiracetam for its favorable drug-interaction profile (Almohaish et al., 2024).

3.4.3. Third-Line Therapy: Managing Refractory Status Epilepticus (RSE)

Anesthetic Infusions: Midazolam, Propofol, and Ketamine: Current third-line practice is based on physiological rationale, observational data, and consensus, given the paucity of RCTs. Midazolam is the most commonly recommended initial anesthetic. Propofol is effective but carries the risk of propofol infusion syndrome with prolonged, high-dose use. Ketamine, an NMDA receptor antagonist, has gained significant traction due to its unique mechanism that theoretically counteracts the pathophysiology of late-stage SE (Heuser et al., 2022; Wieruszewski et al., 2020).

Evidence for Ketamine as an Early Agent in RSE: A systematic review and meta-analysis by Rosati et al. (2021) found that ketamine was associated with seizure termination in 63% of patients with RSE. Importantly, its use was not associated with significant hypotension, making it a favorable agent in patients with hemodynamic instability. Recent reviews advocate for the earlier use of ketamine, either as a primary third-line agent or in combination with midazolam (Gavvala & Brophy, 2024; Joshi & Kapur, 2025).

3.4.4. Novel and Emerging Antiseizure Medications

For super-refractory SE, several novel agents show promise. Brivaracetam, with its higher affinity for the synaptic vesicle protein 2A (SV2A), may offer a benefit in levetiracetam-resistant cases (Gavvala & Brophy, 2024). Perampanel, an AMPA receptor antagonist, addresses a key excitatory pathway in SE. Allopregnanolone (Brexanolone), a neuroactive steroid, is approved for use in SRSE and may help overcome benzodiazepine resistance, but its high cost and complex administration limit widespread use (Gettings et al., 2025).

3.4.5. Synthesis of Major Guideline Recommendations

A systematic review of guidelines by Vignatelli et al. (2024) and Cao et al. (2024) confirms strong consensus on core principles but reveals nuanced differences. Both the Neurocritical Care Society (NCS) and American Epilepsy Society (AES) guidelines, along with the recent American College of Emergency Physicians (ACEP) clinical policy (Smith et al., 2024), endorse:

1. A time-sensitive, staged treatment approach.
2. Benzodiazepines as unequivocal first-line therapy.
3. The equivalence of levetiracetam, fosphenytoin, and valproate as second-line options.

The primary difference lies in the strength of recommendation for specific second-line agents in subpopulations and the sequencing of third-line therapies. All recent guidelines stress the importance of continuous EEG monitoring and simultaneous investigation and treatment of the underlying etiology (O'Kula & Hill, 2024; Besha et al., 2023; Trinka et al., 2015).

4. DISCUSSION:

4.1. Summary of Principal Findings

This systematic review analyzed 18 highly relevant studies, including key Randomized Controlled Trials (RCTs) and modern clinical guidelines, to synthesize the most current evidence regarding the emergency management of Status Epilepticus (SE). The principal findings reinforce the time-sensitive nature of SE treatment and highlight recent paradigm shifts in pharmacological strategy. First, the core evidence for first-line benzodiazepine therapy remains unequivocally strong, demonstrating that rapid pre-hospital administration of agents like lorazepam is paramount for seizure cessation (Alldredge et al., 2001). Second, the therapeutic approach to second-line therapy has been fundamentally reshaped by the Established Status Epilepticus Treatment Trial (ESETT), which established the "three-drug equipoise," showing that levetiracetam, fosphenytoin, and valproate have equivalent efficacy and safety profiles for benzodiazepine-refractory SE (Kapur et al., 2019). Third, in the management of Refractory SE (RSE), ketamine has emerged as a promising anesthetic agent, with systematic reviews reporting high efficacy rates and favorable hemodynamic profiles (Rosati et al., 2021). Finally, a synthesis of major guidelines reveals a strong consensus on a time-sensitive, staged approach to therapy, emphasizing rapid intervention to prevent neurological injury and improve outcomes.

4.2. Interpretation of the Evidence and Clinical Implications

4.2.1. The Paradigm Shift in Second-Line Therapy Selection

The most profound change in SE management has been the shift away from phenytoin as the default second-line agent. The ESETT trial provided high-quality evidence for the "three-drug equipoise," fundamentally altering clinical practice (Kapur et al., 2019; Vignatelli et al., 2024; Smith et al., 2024). This paradigm shift empowers clinicians to select an agent based on patient-specific factors rather than historical precedent. Levetiracetam offers a favorable safety profile and minimal drug interactions, making it suitable for complex patients (Almohaish et al., 2024). Valproate may be preferred in certain genetic epilepsies but must be avoided in patients with suspected liver dysfunction. Fosphenytoin remains a viable option, particularly where familiarity and cost are considerations. This flexibility allows for more personalized and potentially safer care in the hectic ED environment and emphasizes the importance of institutional protocols that prioritize rapid administration over adherence to a single, rigid drug sequence.

4.2.2. The Rationale for Early Escalation and the Role of Ketamine

The pathophysiological understanding of SE progression from a compensated to a refractory state, mediated by GABAA receptor internalization and NMDA receptor upregulation, provides the scientific basis for rapid treatment escalation (Chen & Wasterlain, 2006; Naylor et al., 2005; Joshi & Kapur, 2025). Delays at any stage are a primary predictor of poor outcomes (Sutter et al., 2013). In RSE, the evidence supports the early introduction of ketamine (Rosati et al., 2021). Its unique mechanism as an NMDA antagonist directly targets the late-stage pathophysiology of SE, a distinct advantage over GABA-ergic agents like midazolam and propofol to which the brain becomes pharmacoresistant (Heuser et al., 2022; Wieruszewski et al., 2020). Its hemodynamic stability profile makes it an ideal agent for patients in septic or cardiogenic shock, common comorbidities in critically ill SE patients (Gavvala & Brophy, 2024), suggesting that NMDA antagonists should be considered earlier in the treatment cascade.

4.2.3. The Potential for Novel Agents to Address Treatment Gaps

For patients with super-refractory status epilepticus (SRSE), where conventional therapies fail, novel agents offer a crucial lifeline. Brivaracetam's higher SV2A binding affinity may provide efficacy in some levetiracetam-resistant cases, though robust data is still needed (Gavvala & Brophy, 2024). Perampanel's action on the AMPA receptor provides a novel mechanism to counter glutamate-mediated excitotoxicity (Almohaish et al., 2024). Most notably, allopregnanolone (brexanolone) represents a breakthrough as the first drug specifically approved for SRSE, offering a mechanism to modulate both synaptic and extrasynaptic GABA receptors and potentially restore inhibitory tone (Gettings et al., 2025). While cost and administration challenges exist, these agents signify a move towards mechanism-specific treatments for the most severe forms of SE and highlight the evolving landscape initially described by Shorvon & Ferlisi (2011).

4.3. Limitations of the Included Evidence

Despite these advances, significant limitations in the evidence base remain. A primary challenge is the heterogeneity in RSE studies. The lack of standardized definitions, varied etiologies, and diverse prior treatment regimens make it difficult to compare outcomes across observational studies and small trials (Sutter et al., 2024). Furthermore, there is a critical lack of long-term outcome data. While most trials and guidelines focus on short-term seizure cessation, data on functional recovery, cognitive outcomes, and quality of life months or years after the incident are scarce (Joshi & Kapur, 2025; Hesdorffer et al., 1998). This gap makes it challenging to fully assess the impact of different management strategies on patients' lives beyond hospital discharge, as the true success of an SE protocol must be measured by the patient's eventual quality of life.

4.4. Limitations of the Present Review

This review is subject to several limitations. The exclusion of non-English publications introduces a potential for language bias, possibly omitting relevant studies. While the search was comprehensive, the potential for publication bias remains, as negative or inconclusive studies may be less likely to be published (Cao et al., 2024). Furthermore, by focusing on high-level evidence and major guidelines to ensure quality, some relevant observational data or smaller clinical experiences may have been excluded, potentially limiting the scope of clinical scenarios covered.

4.5. Implications for Practice and Policy

The synthesized evidence strongly supports the implementation of standardized, protocol-driven care for SE in the ED. Institutions should develop and implement structured algorithms that emphasize:

1. Time-sensitive intervention: Mandating rapid administration of benzodiazepines within 5 minutes and predefined second-line agents within strict time frames (Betjemann et al., 2019; Smith et al., 2024).
2. Choice and access: Ensuring immediate pharmacy access to all three second-line agents (levetiracetam, fosphenytoin, valproate) to facilitate clinician choice based on the three-drug equipoise.
3. Early escalation: Defining clear triggers for escalating to third-line anesthetic therapy and encouraging the early consideration of ketamine.
4. System-based approach: Integrating neurology consultation, ICU transfer, and continuous EEG monitoring into the protocol to ensure seamless care (O'Kula & Hill, 2024; Besha et al., 2023).
5. Adherence to standardized, staged protocols, built on the evidence from ESETT and pre-hospital trials, is the most effective policy measure to improve patient outcomes by mitigating treatment delay.

4.6. Recommendations for Future Research

To address the existing evidence gaps, future research should prioritize:

1. Trials in Super-Refractory SE: There is an urgent need for randomized controlled trials in SRSE to compare the efficacy of novel agents (e.g., brivaracetam, perampanel, allopregnanolone) and combination therapies against standard anesthetic regimens, including head-to-head RCTs of midazolam versus ketamine.
2. Novel Agent Sequencing: Research should investigate the optimal sequencing and combination of novel and established agents in RSE and SRSE to develop evidence-based treatment pathways (Madhiyazhagan, 2021).
3. Long-Term Outcomes: Future studies must incorporate long-term functional, cognitive, and quality-of-life outcomes as primary endpoints to truly gauge therapeutic success (Trinka et al., 2015).
4. Biomarker-Driven Therapy: Exploring biomarkers that can predict response to specific therapies (e.g., GABAergic vs. NMDA antagonist) could pave the way for personalized medicine in SE management (Joshi & Kapur, 2025).

5. CONCLUSION:

The management of status epilepticus in the emergency department is a time-critical endeavor where initial interventions profoundly influence patient outcomes. This systematic review consolidates the robust evidence underpinning the modern, staged treatment approach. The

unequivocal efficacy of rapid benzodiazepine administration remains the cornerstone of emergent therapy, a principle firmly established by trials such as Alldredge et al. (2001). The landscape of second-line therapy has been fundamentally reshaped by the ESETT trial, which established the therapeutic equipoise among levetiracetam, fosphenytoin, and valproate, empowering clinicians to make patient-tailored choices (Kapur et al., 2019).

For cases progressing to refractory status epilepticus (RSE), the evidence supports the early integration of ketamine, an NMDA antagonist whose mechanism directly targets the late-stage pathophysiology of SE and offers hemodynamic stability (Rosati et al., 2021; Heuser et al., 2022). Furthermore, novel agents like brivaracetam, perampanel, and allopregnanolone provide crucial options for super-refractory cases, signifying a move towards mechanism-specific treatments (Gettings et al., 2025; Gavvala & Brophy, 2024).

Synthesis of major guidelines reveals a strong consensus on this time-sensitive, protocol-driven pathway, emphasizing that delays at any stage are a primary modifiable risk factor for poor outcomes (Sutter et al., 2013; Smith et al., 2024). Therefore, the most effective strategy to improve survival and neurological recovery is the consistent implementation of standardized ED protocols that mandate rapid medication administration and timely escalation of care. Future research must now focus on randomized trials in super-refractory SE, the optimal sequencing of novel agents, and the critical evaluation of long-term functional outcomes to fully gauge the success of our therapeutic interventions (Trinka et al., 2015; Joshi & Kapur, 2025).

REFERENCES:

1. Alldredge, B. K., Gelb, A. M., Isaacs, S. M., Corry, M. D., Allen, F., Ulrich, S., ... & Lowenstein, D. H. (2001). A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *The New England Journal of Medicine*, *345*(9), 631–637.
2. Almohaish, S., Tesoro, E. P., & Brophy, G. M. (2024). Status epilepticus: an update on pharmacological management. *Seminars in Neurology*, *44*(3), 324–332.
3. Au, C. C., Branco, R. G., & Tasker, R. C. (2017). Management protocols for status epilepticus in the pediatric emergency room: systematic review article. *Jornal de Pediatria*, *93*(Suppl 1), 84-94.
4. Besha, A., Adamu, Y., Mulugeta, H., Zemedkun, A., & Destaw, B. (2023). Evidence-based guideline on management of status epilepticus in adult intensive care unit in resource-limited settings: a review article. *Annals of Medicine and Surgery*, *85*(6), 2714-2720.
5. Betjemann, J. P., & Lowenstein, D. H. (2015). Status epilepticus in adults. *The Lancet Neurology*, *14*(6), 615–624.
6. Betjemann, J. P., Josephson, S. A., Lowenstein, D. H., & Guterman, E. L. (2019). Emergency medical services protocols for generalized convulsive status epilepticus. *JAMA*, *321*(12), 1216-1217.
7. Cao, Y., Li, H., Chen, M., Wang, P., Shi, F., Zhu, X., ... & Chen, L. (2024). Evaluation and systematic review of guidance documents for status epilepticus. *Epilepsy & Behavior*, *150*, 109555.
8. Chen, J. W., & Wasterlain, C. G. (2006). Status epilepticus: pathophysiology and management in adults. *The Lancet Neurology*, *5*(3), 246–256.
9. Gavvala, J. R., & Brophy, G. M. (2024). Newer Antiseizure Medications for the Treatment of Status Epilepticus in the Intensive Care Unit. *Seminars in Neurology*, *44*(1), 92–106.
10. Gettings, J. V., Chafjiri, F. M. A., Patel, A. A., Shorvon, S., Goodkin, H. P., & Loddenkemper, T. (2025). Diagnosis and management of status epilepticus: improving the status quo. *The Lancet Neurology*, *24*(1), 65-76.
11. Haider, H. A. (2025). Initial Management of Acute Seizures and Status Epilepticus. *Medical Clinics*, *109*(2), 497-508.
12. Hesdorffer, D. C., Logroscino, G., Cascino, G., Annegers, J. F., & Hauser, W. A. (1998). Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. *Neurology*, *50*(3), 735–741.
13. Heuser, K., Olsen, K. B., Ulvin, L. B., Gjerstad, L., & Taubøll, E. (2022). Modern treatment of status epilepticus in adults. In *Epilepsy* (pp. 55-78). Exon Publications.
14. John, R., Grahf, D., Lochner, A., Taylor, R., Krupp, S., & Vohra, T. (2022). Evaluation and treatment of adult status epilepticus in the emergency department. *Current Emergency and Hospital Medicine Reports*, *10*(4), 107-115.
15. Joshi, S., & Kapur, J. (2025). Status epilepticus: Updates on mechanisms and treatments. *Epilepsia Open*.
16. Kapur, J. (2025). Strategies to innovate emergency care of status epilepticus. *Neurotherapeutics*, *22*(1), e00514.
17. Kapur, J., Elm, J., Chamberlain, J. M., Barsan, W., Cloyd, J., Lowenstein, D., ... & Silbergleit, R. (2019). Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. *The New England Journal of Medicine*, *381*(22), 2103–2113.
18. Krumholz, A., Wiebe, S., Gronseth, G. S., Gloss, D. S., Sanchez, A. M., Kabir, A. A., ... & French, J. A. (2015). Evidence-based guideline:

management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*, *84*(16), 1705-1713.
19. Lowenstein, D. H., Bleck, T., & Macdonald, R. L. (1999). It's time to revise the definition of status epilepticus. *Epilepsia*, *40*(1), 120–122.
20. Madhiyazhagan, M. (2021). Time is brain: Review of emergency management of status epilepticus in adults. *Current Medical Issues*, *19*(4), 269-273.
21. Messahel, S., Bracken, L., & Appleton, R. (2022). Optimal management of status epilepticus in children in the emergency setting: a review of recent advances. *Open Access Emergency Medicine*, *14*, 491-506.
22. Naylor, D. E., Liu, H., & Wasterlain, C. G. (2005). Trafficking of GABAA receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *The Journal of Neuroscience*, *25*(34), 7724–7733.
23. O'Kula, S. S., & Hill, C. E. (2024). Improving quality of care for Status Epilepticus: putting protocols into practice. *Current Neurology and Neuroscience Reports*, *24*(9), 373-379.
24. Penberthy, L. T., Towne, A., Garnett, L. K., Perlin, J. B., & DeLorenzo, R. J. (2005). Estimating the economic burden of status epilepticus to the health care system. *Seizure*, *14*(1), 46–51.
25. Pinto, L. F., Oliveira, J. P. S. D., & Midon, A. M. (2022). Status epilepticus: review on diagnosis, monitoring and treatment. *Arquivos de neuro-psiquiatria, 80*, 193-203.
26. Poblete, R., & Sung, G. (2017). Status epilepticus and beyond: a clinical review of status epilepticus and an update on current management strategies in super-refractory status epilepticus. *Korean Journal of Critical Care Medicine*, *32*(2), 89-105.
27. Rosati, A., De Masi, S., & Guerrini, R. (2021). Ketamine for Refractory Status Epilepticus: A Systematic Review and Meta-Analysis. *Frontiers in Neurology*, *12*, 653674.
28. Shorvon, S., & Ferlisi, M. (2011). The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*, *134*(Pt 10), 2802–2818.
29. Smith, M. D., Sampson, C. S., Wall, S. P., Diercks, D. B., Anderson, J. D., Byyny, R., ... & Vandertulip, K. (2024). Clinical policy: critical issues in the management of adult patients presenting to the emergency department with seizures. *Annals of Emergency Medicine*, *84*(1), e1-e12.
30. Sutter, R., Kaplan, P. W., & Rüegg, S. (2024). Outcome and predictors of outcome in refractory status epilepticus. *Current Opinion in Critical Care*, *30*(2), 112–119.
31. Sutter, R., Marsch, S., Fuhr, P., & Rüegg, S. (2013). Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. *Epilepsia*, *54*(3), 502–511.
32. Trinka, E., Cock, H., Hesdorffer, D., Rossetti, A. O., Scheffer, I. E., Shinnar, S., Shorvon, S., & Lowenstein, D. H. (2015). A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*, *56*(10), 1515–1523.
33. Vezzani, A., Fujinami, R. S., White, H. S., Preux, P. M., Blümcke, I., Sander, J. W., & Löscher, W. (2016). Infections, inflammation and epilepsy. *Acta Neuropathologica*, *131*(2), 211–234.
34. Vignatelli, L., Tontini, V., Meletti, S., Camerlingo, M., Mazzoni, S., Giovannini, G., ... & Di Vito, L. (2024). Clinical practice guidelines on the management of status epilepticus in adults: A systematic review. *Epilepsia*, *65*(6), 1512-1530.
35. Wasterlain, C. G., & Chen, J. W. (2008). Mechanistic and pharmacologic aspects of status epilepticus and its treatment with new antiepileptic drugs. *Epilepsia*, *49*(Suppl 9), 63–73.
36. Wieruszewski, E. D., Brown, C. S., Leung, J. G., & Wieruszewski, P. M. (2020). Pharmacologic management of status epilepticus. *AACN Advanced Critical Care*, *31*(4), 349-356.